NTP
National Toxicology Program

NTP Retreat
October 19-20, 2006
NC Biotechnology Center

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NTP Board of Scientific Counselors

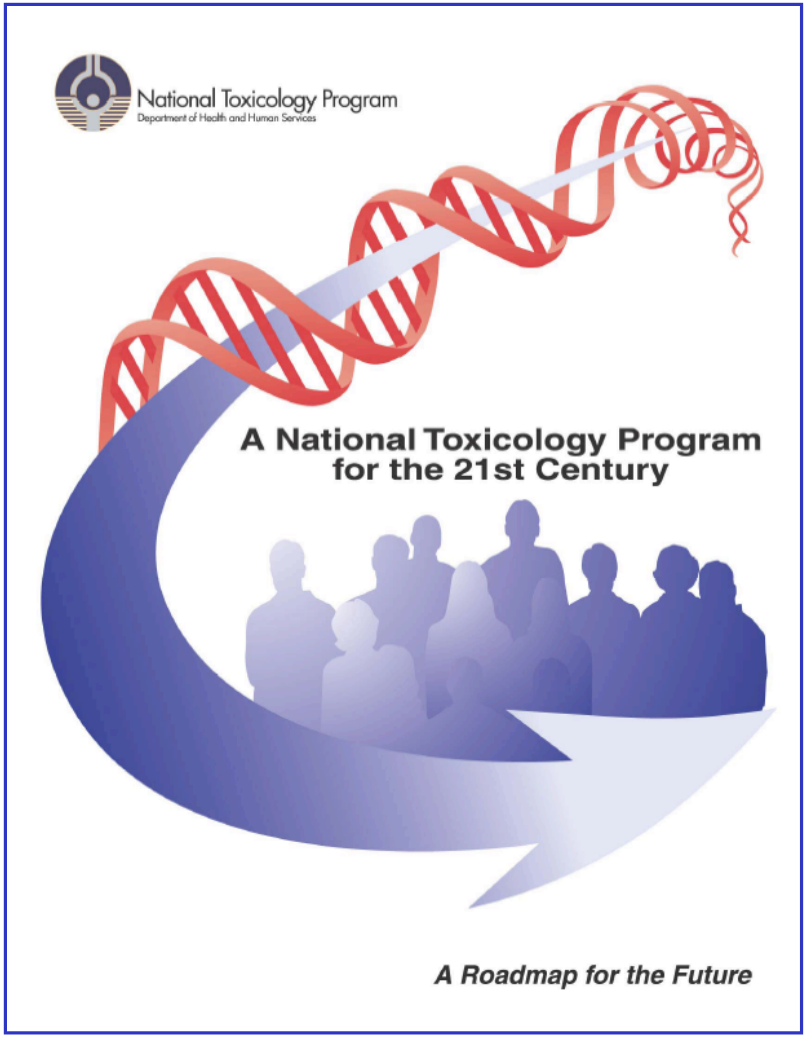
December 1, 2006

NTP Mission

- Coordinate toxicology testing programs within the federal government.
- Strengthen the science base in toxicology.
- Develop and validate improved testing methods.
- Provide information about potentially toxic chemicals to health, regulatory, and research agencies, scientific and medical communities, and the public.

NTP Roadmap

- Refine traditional toxicology assays.
- Expand and evaluate the use of mechanistic and shorter term assays for hazard identification.
- Improve overall utility of NTP products for public health decision-making.



Retreat Purpose

- To make decisions to aid the NTP in its progress with the Roadmap for Toxicology in the 21st Century.
- To evaluate the current position of the Program in meeting the roadmap objectives.
- To implement the outcomes of various NTP Roadmap workshops and initiatives to assess where we can incorporate findings and recommendations into our current activities, studies, and designs.
- To evaluate the impact to the Program of any changes to current practices, with the overall aim to make the Program more effective and efficient.

Crosscutting Questions

- Informatics?
  - High Throughput Screening
  - Database crosstalk
- What are expertise and resource needs?
- How do we better connect to NIEHS and other partners?
- How to optimize external input?
- How to work more effectively and efficiently?
  - Can we better communicate/integrate across NTP?
  - Are there opportunities to streamline operations/processes?

Organizing Committee

- Paul Foster, chair
- June Dunnick
- Jef French
- Dori Germolec
- Angela King-Herbert
- Dave Malarkey
- Barbara Shane
- Ray Tice
- Greg Travlos
- Nigel Walker

Breakout Chairs & Rapporteurs

- Michelle Hooth
- Ruth Lunn
- Rachel Patterson
- Kris Thayer
- Michael Wyde

Retreat Topics

- Pathology review
- Strains and host susceptibility
- Reproductive tumors and in utero exposures
- High throughput screening
- Biomarkers
- NTP process and study design


CAUTION
WATER ON ROAD
DURING
RAIN

Pathology Review

- Pathology data
  - 2 year bioassay: 800 animals and ~40,000 tissues
  - 90 day study: 240 animals and ~10,000 tissues
- Pathology review process (2 year studies)
  - Pathology Data Review (PDR)
  - Audit of Pathology Specimens (APS)
  - Quality Assessment (QA)
  - Pathology Working Group (PWG)
- Recommendations
  - Use digital images for virtual PWG; virtual or electronic conferences; consider scope on case-by-case basis.
  - Some redundancies; resolve discrepancies earlier.
  - Enhance path review for noncancer toxicity studies.

Strains and Host Susceptibility

- Rat
  - Do not continue to utilize F344 rat. Changes in phenotype over time (reproductive problems, high background tumor incidence) have limited its usefulness.
  - Use Wistar Han or strain appropriate for study.
- Mouse
  - B6C3F1 provides good spectrum of tumor susceptibility.
  - Multiple mouse strains to examine genetic diversity in Host Susceptibility Initiative and possibly in 2 year studies.

Reproductive Tumors and In Utero Exposures

- Strains
  - F344 is insensitive model for certain types of tumors (i.e., testicular tumors, mammary gland fibroadenomas).
  - Consider use of different models to detect effects when appropriate (e.g. post-pregnancy exposure, alternative model when prostate is a suspected target site).
- Developmental programming
  - Incorporate in utero-perinatal dosing.
  - Build database on early in life exposure.
  - Certain tumor types require perinatal exposures (e.g., brain, germ cell tumors).

High Throughput Screening

- NTP nominations should be evaluated by HTS as a means of prioritizing further studies.
- Recognize limitations of HTS (e.g., solvents, volatility, dose, ADME).
- Milestones
  - Success based on predictive capacity of a battery of HTS assays for a given endpoint.
  - Compare to and correlate with conventional in vivo assays.
  - Validation needed to replace in vivo assays.
- First priority is to develop HTS assays that evaluate relevant pathways (e.g., developmental, immunological, DNA damage, cell death).
- Data management/analysis
  - Mine data for predictive relationships within or between classes of compounds.

Biomarkers

- Lung
  - BAL, cytokines when lung is target organ.
- Heart
  - Cardiac troponin.
  - B-type natriuretic peptide needs more development and validation.
- Lipid/carbohydrate
  - Serum fructosamine for detection of insulin resistance.
  - Requires validation to assess effect of nutritional status.
- Evaluate performance of any biomarker added.

NTP Process and Study Design

- Develop criteria for determining public health impact of a proposed nomination (vs the current agent-oriented criteria).
- Develop a proactive campaign to develop nominations of high public health significance.
- Conduct regular review of NTP activities by research topics and current directions vs agent by agent.
  - Coordination of science across multiple staff and studies/projects.
  - Integration of endpoints, pathology, modeling etc.
- Develop consistent electronic data collection tools/formats across study/data types.
  - Current IT tools are disconnected. Data is currently not stored in an easily accessible format.
- Recruit expertise outside of NTP to ensure sufficient breadth and depth of personnel and knowledge.

Next Steps

- Pathology review
  - Enhance digital imagining capacity and electronic exchange.
- Strains and host susceptibility
  - Implementation group to handle logistics of changing rat strain.
  - Move host susceptibility into reality in FY07.
- Reproductive tumors and in utero exposures
  - Perinatal dosing regimen.
- High throughput screening
  - Enhance data analysis and interaction with NCGC.
- Biomarkers
  - Validate methods for troponin, inflammation markers in BAL, and fructosamine.
- NTP process and study design
  - Implementation group to evaluate nomination process.